

Subject: [NTP Web] Report on Carcinogens Public Comments Submission
[72FR63900 - 63901]

Name: Dr. Bojan Jelakovic

Email: bojan.jelakovic@zg.htnet.hr

Company / Affiliation: U of Zagreb School of Medicine

Comments: 1. Endemic (Balkan) nephropathy (EN) and aristolochic acid nephropathy (AAN) are in fact the same disease.

Both syndromes have similar clinical characteristics, pathological findings, accumulation of aristolactam- DNA adducts and share a unique p53 mutational spectrum. Approximately the same percentage (3-5%) of exposed persons develop EN and AAN and, in both entities, share a high incidence of the uncommon upper urothelial (transitional) cell carcinoma. According to the recent report by Miletić-Medved et al,(2005), the specific mortality of upper urothelial cancers in the endemic region is 55 times higher than in other parts of Croatia or Europe. More than 50 upper urothelial cancer cases from EN area per year were operated on in Croatia over the past 30 years (Medverec 2006) EN and AAN appear to be caused with the same chemical carcinogen; the only difference being duration of clinical course. In AAN, larger amounts of aristolochic acid were ingested in a short period of time while in EN smaller doses were ingested over a long period.

2. Farmers from the EN region in Croatia ingested AA as a contaminant of bread--it is not used in this area for medicinal purposes

A.clematitis is found in wheat fields in the endemic region and little effort was made to remove seeds from this plant from the harvested wheat grain. Although farmers noted that contaminated bread had a bitter taste, they ate it anyway. Farmers in a different EN region (Serbia) reported

similar experience. In an epidemiologic survey performed in 2005 in Croatia (manuscript in preparation), we looked for--but failed to find -- any evidence that farmers used A.clematitis or Asarum as an herbal tea. In this study, 1041 inhabitants of three Croatian EN villages responded negatively to a series of questions as to whether they used those plants, or parts of them, as herbal remedies.

We conclude that, in EN, where there is strong evidence of exposure to AA, including the fingerprint mutation in the p53 gene of urothelial tumors (Grollman et al, 2007), AA is a persistent dietary contaminant. This is the first direct evidence that such exposure exists and argues strongly that naturally occurring mixtures of AA are carcinogenic to humans. I suggest that this information be included in the discussion section of the NTP Report.

3. Nephrotoxic effects on farm animals (horses) following ingestion of Aristolochia clematitis plants More than 50 years ago, the toxic effects of Aristolochia on horses was described in detail. Two of the most comprehensive papers originated in Croatia (Dumić,1954, in Croatian; and Martinčević, 1957, in German). In those reports authors described epidemiology, exposure, clinical course and the dose dependent effect of AA. Remarkably, pathological findings in horses were similar to those described for EN, and AAN in humans. The horses had been fed hay and straw contaminated with A.clematitis. This observation is in line with my

conclusion (see #2) that aristolochic acid from natural sources has the same toxic effect as botanical products containing this chemical.

4. Other comments:

P 58 line 1 - countries harboring with EN should be listed in alphabetic order

P 58 line 1 - EN is, in fact, a "familial" disease but this description could be misinterpreted to suggest an "inherited "disease. EN has a mosaic distribution in river valleys (some villages affected the others not) inside EN villages (some households affected, others not) and within EN families (some members affected while others are not).

Differences between villages reflects different levels of exposure, most probably because of differences in prevalence of Aristolochia. Differences between households could be the consequence of differences in eating habits, while the difference within households undoubtedly reflects genetic predisposition to the effect of this environmental carcinogen. I recommend that you change the word "familial" to "household" and include this commentary in your discussion of EN.